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MULTICOMPONENT MW ASSISTED SYNTHESIS OF 3-THIOXO-1,2,4-TRIAZIN-5-ONE DERIVATIVES AS PROMISING AGENT IN FIBROSIS TREATMENT

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ABSTRACT

Triazine is a six member heterocyclic ring system having three nitrogen atoms. Many 1,2,4- triazine derivatives involve in several biological processes and serve as medicinally interesting compounds as they show a broad spectrum of antimicrobial activity such as anti-protozoals, anti-cancer, estrogen receptor modulator,anti-virals, and anti-malerials. Keeping in view the high pharmacological importance we report here a synthesis of several 4-substituted-3-thioxo-1,2,4-triazin-5-one derivatives using environmentally benign protocol where, neat reactants are subjected to microwave irradiation. The synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR, mass spectral data and elemental analysis. The confirmed structures were subjected to PASS for their probabilities of being biologically active. Biological prediction study of these derivatives was done using computer programme PASS to find out the most active molecules. Short reaction time, good yield (69-85%), simple workup procedure are the remarkable features of this protocol.

KEYWORDS: 3-thioxo-1,2,4-triazin-5-one, Biological Prediction Study, Microwave Irradiation.

INTRODUCTION

The triazine structure is a heterocyclic ring, analogous to the six-membered benzene ring but with three carbons replaced by nitrogens. The three isomers of triazine are distinguished from each other by the positions of their nitrogen atoms, and are referred to as 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine of which, 1,3,5-Triazine nucleus is more significant in pharmaceutical, medicinal, biochemical, industrial, and agricultural sciences. These moeties showed muscle relaxant[1], hypoglycemic[2], blood pressure depressant[3], anti-diabetic[4] properties. They also showed anti-tumor[5], anti-bacterial[6], anti-inflammatory[7], anti-cancer[8], and anti-psychotic properties[9]. Some of them are used in industries as finishing and brightening agents[10]. They are also been used as herbicidal[11-12], sea water algicidal[13], fungicidal[14], insecticidal[15] and pesticidals[16]. The synthesis of 3-thioxo-1,2,4-triazin-5-one derivatives involves one pot three component procedure as multi component reaction (MCRs) are of increasing importance in organic and medicinal chemistry. Biological predictions are done using computer programme PASS.

PASS

Each biologically active compound reveals a wide variety of biological actions in biological systems (human organisms, animals, in vivo and in vitro assays). It is practically impossible to study each compound in all tests currently available. Therefore, the ability to select compounds with required types of biological activity and without unwanted adverse effects and toxicity is very desirable.

The software PASS (Prediction of Activity Spectra for Substances) was developed by Pharma Expert toward this purpose. PASS predicts biological activity spectra on the basis of structural formulae of chemical compounds. The biological activity of compounds is predicted on the basis of structure-activity relationships of known biological active substances presented in the training set. PASS 1.602 training set includes 45649 substances. PASS 1.602 can predict 1043 different types of biological activities including pharmacological effects, biochemical mechanisms, carcinogenicity, mutagenicity and teratogenicity. The mean prediction of accuracy in leave one out cross-validations of PASS is about 85%.

MATERIALS AND METHODS

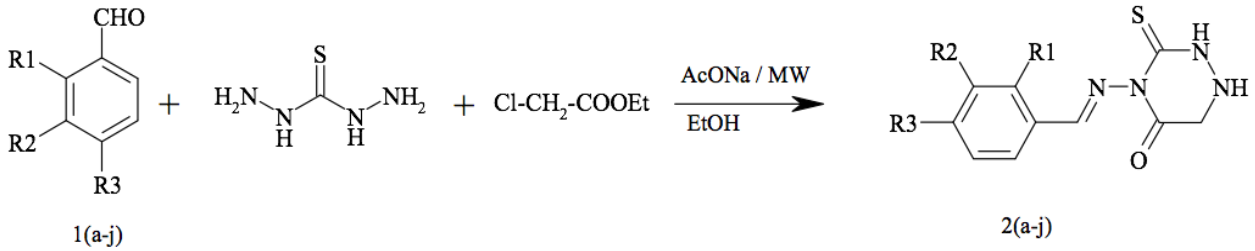
Purity of the compounds were checked by TLC on silica-G plates. Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. Biological prediction studies have been carried out using computer

programme PASS.

General procedure for the synthesis of *4-{[1-aryl-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 a-j)*

A mixture of thiocarbohydrazide (1.06 g, 0.01 mole), aromatic aldehyde (0.01 mole), ethyl chloroacetate (1.06 g, 0.01 mole) anhydrous sodium acetate(1.64 g , 0.02 mole) were added in absolute ethanol and irradiated with microwaves at 40% microwave power (140 W) for 3 mins. The reaction mixture was poured on ice to obtain the product. The separated product was filtered, and recrystallized from ethanol. [(2a) m.p. 270^{o}C, yield (70%)].

Scheme-I



RESULTS AND DISCUSSION

The ten different 3-thioxo-1,2,4-triazin-5-one derivatives were synthesized by reacting mixture of thiocarbohydrazide, various substituted aromatic aldehydes, ethyl chloroacetate & anhydrous sodium acetate in absolute ethanol by irradiation with microwaves at 40% microwave power (140 W) for 3-6 mins. The reaction mixture was poured on ice to obtain the products 2 (b-j). Their physical and analytical data are recorded in Table-I.

Table 1: physical and analytical data

Comp.	R_1	R_2	R_3	Time (in min.)	Yield %	M.P. ^{o}C	Mol. Formula (Molar Mass)	Elemental Analysis Found(Calcd)%			
								C	H	N	S
2-a	H	H	H	3	70	270	$C_{10}H_{10}N_4OS$ 234	51.26 (51.27)	4.30 (4.32)	23.93 (23.94)	13.69 (13.70)
2-b	Cl	H	H	3	75	230	$C_{10}H_9N_4OSCl$ 268	44.70 (44.74)	3.38 (3.45)	20.85 (20.90)	11.93 (12.00)
2-c	H	H	Cl	4	78	238	$C_{10}H_9N_4OSCl$ 268	44.70 (44.74)	3.38 (3.50)	20.85 (20.90)	11.93 (12.00)
2-d	H	H	OCH_3	5	84	242	$C_{11}H_{12}N_4O_2S$ 264	49.99 (44.99)	4.58 (4.70)	21.20 (21.70)	12.13 (12.85)
2-e	H	H	OC_2H_5	5	79	245	$C_{12}H_{14}N_4O_2S$ 278	51.78 (51.80)	5.07 (5.09)	20.13 (20.14)	11.52 (11.56)
2-f	H	H	CH_3	6	85	255	$C_{11}H_{12}N_4OS$ 248	53.21 (51.23)	4.87 (4.90)	22.56 (22.80)	12.91 (12.98)
2-g	H	H	OH	4	77	233	$C_{10}H_{10}N_4O_2S$ 518	47.99 (48.02)	4.03 (4.05)	22.39 (23.45)	12.81 (12.90)
2-h	H	Cl	H	3	79	249	$C_{10}H_9N_4OSCl$ 268	44.70 (44.80)	3.38 (3.45)	20.85 (20.95)	11.93 (11.99)
2-i	H	Br	H	5	81	267	$C_{10}H_9N_4OSBr$ 313	38.35 (38.40)	2.90 (2.95)	25.51 (25.90)	10.24 (10.29)
2-j	H	NO_2	H	6	69	252	$C_{10}H_9N_5O_3S$ 279	43.01 (43.08)	3.35 (3.40)	25.08 (25.09)	11.48 (11.50)

The structures were confirmed by IR, PMR, ^{13}CNMR spectral and elemental analysis data.

Spectral data of compounds (2a-j):

4-{[1-phenyl-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 a)

IR ν_{max}: 3369(N-H), 1618(C=O), 1576(CH=N), 1326(C=S) cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 3.77(s, 2H, CH_2), 5.01(s, 1H, NH), 9.38(s, 1H, NH), 7.98(s, 1H, CH=N), 7.69-7.71(d, 2H, Ar-H_c), 7.17-7.21(t, 2H, Ar-H_b), 6.91-6.94(t, 1H, Ar-H_a).
^{13}CNMR ($CDCl_3$): δ 49.80, 121.34, 122.30, 128.27, 140.85, 162.36, 209.54, and 212.24.
MS (m/z): 234.2 (M+)

4-{[1-(2-Chloro-phenyl)-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 b)

IR ν_{max}: 3369(N-H), 1618(C=O), 1576(CH=N), 1326(C=S), 625(C-Cl) cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 3.82(s, 2H, CH_2), 5.01(s, 1H, NH), 9.44(s, 1H, NH), 9.10(s, 1H, CH=N), 7.36-7.46(m, 3H, Ar-H), 8.22-8.24(d, 1H, Ar-H).
^{13}CNMR ($CDCl_3$): δ 49.80, 127.04, 128.27, 130.04, 132.18, 135.81, 159.09, 209.54 and 212.24.
MS (m/z): 268.01 (M+)

4-{[1-(4-Chloro-phenyl)-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 c)

IR ν_{max}: 3369(N-H), 1618(C=O), 1576(CH=N), 1326(C=S), 625(C-Cl) cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 3.77(s, 2H, CH_2), 5.01(s, 1H, NH), 9.93(s, 1H, NH), 7.98(s, 1H, CH=N), 7.44-7.46(d, 2H, Ar-H_a), 7.87-7.89(d, 2H, Ar-H_b).
^{13}CNMR ($CDCl_3$): δ 49.80, 128.82, 129.18, 133.51, 134.24, 140.80, 209.51, and 210.24.
MS (m/z): 268.01 (M+)

4-{[1-(4-Methoxy-phenyl)-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 d)

IR ν_{max}: cm^{-1}. 1014(-OCH_3), 3370(N-H), 1622(C=O), 1590(CH=N), 1320(C=S) cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 3.89 (s, 3H, OCH_3), 3.77(s, 2H, CH_2), 5.01(s, 1H, NH), 9.93(s, 1H, NH), 7.98(s, 1H, CH=N), 7.14-7.16(d, 2H, Ar-H_a), 7.44-7.46(d, 2H, Ar-H_b).
^{13}CNMR ($CDCl_3$): δ 48.65, 55.48, 121.97, 124.51, 127.55, 128.93, 159.09, 211.94, and 214.55.
MS (m/z): 264.30 (M+)

4-{[1-(4-Ethoxy-phenyl)-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 e)

IR ν_{max}: 1010(-O-), 3364(N-H), 1620(C=O), 1594(CH=N), 1322(C=S) cm^{-1}.
^{1}HNMR ($CDCl_3$):1.18-1.25 (t, 3H, -CH_3), 3.77-3.86(q, 2H, -CH_2-), 3.60(s, 2H, CH_2), 4.51(s, 1H, NH), 9.00(s, 1H, NH), 8.51(s, 1H, CH=N), 6.79-6.83(d, 2H, Ar-H_a), 7.05-7.10(d, 2H, Ar-H_b).
^{13}CNMR ($CDCl_3$): δ 18.09, 48.65, 67.42, 121.97, 124.51, 127.55, 128.93, 159.09, 211.94, 214.55.
MS (m/z): 278.33 (M+)

3-Thioxo-4-{[1-p-tolyl-meth-(E)-ylidine]-amino}-[1,2,4]triazinan-5-one (2 f)

IR ν_{max}: 3300(N-H), 1620(C=O), 1606(CH=N), 1330(C=S) cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 1.48(s, 3H, CH_3), 3.77(s, 2H, CH_2), 5.01(s, 1H, NH), 9.93(s, 1H, NH), 8.51(s, 1H, CH=N), 6.79-6.83(d, 2H, Ar-H_a), 7.61-7.65(d, 2H, Ar-H_b).
^{13}CNMR ($CDCl_3$): δ 22.70, 49.42, 127.52, 128.18, 130.01, 132.24, 135.40, 210.41, and 211.22.
MS (m/z): 248.30 (M+)

4-{[1-(4-Hydroxy-phenyl)-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 g)

IR ν_{max}: 33.15(C-OH), 3350(N-H), 1622(C=O), 1520(CH=N), 1332(C=S) cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 3.70(s, 2H, CH_2), 4.46(s, 1H, NH), 9.57(s, 1H, NH), 8.57(s, 1H, CH=N), 6.82-6.86(d, 2H, Ar-H_a), 7.73-7.77(d, 2H, Ar-H_b), 9.84(s, 1H, OH).
^{13}CNMR ($CDCl_3$): δ 48.47, 125.55, 126.24, 127.25, 128.42, 129.48, 133.51, 140.80, 209.51, and 210.24.
MS (m/z): 518.0 (M+)

4-{[1-(3-Chloro-phenyl)-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 h)

IR ν_{max}: 692(C-Cl), 3289(N-H), 1630(C=O), 1626(CH=N), 1340(C=S) cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 3.72(s, 2H, CH_2), 5.01(s, 1H, NH), 9.56(s, 1H, NH), 8.70(s, 1H, CH=N), 7.60-8.04(m, 4H, Ar-H).
^{13}CNMR ($CDCl_3$): δ 47.52, 126.28, 127.26, 127.52, 128.68, 130.71, 133.27, 135.50, 207.31, and 211.72.
MS (m/z): 268.01 (M+)

4-{[1-(3-Bromo-phenyl)-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 i)

IR ν_{max}: 653(C-Br), 3290(N-H), 1632(C=O), 1676(CH=N), 1338(C=S) cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 3.70(s, 2H, CH_2), 5.02(s, 1H, NH), 9.50(s, 1H, NH), 8.50(s, 1H, CH=N), 7.75-8.30(m, 4H, Ar-H).
^{13}CNMR ($CDCl_3$): δ 52.32, 124.23, 125.14, 128.45, 129.23, 130.51, 133.24, 135.80, 209.20, and 211.22.
MS (m/z): 313.18 (M+)

4-{[1-(3-Nitro-phenyl)-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2 j)

IR ν_{max}: 1350, 1550(Ar-NO_2), 3330(N-H), 1626(C=O), 1606(CH=N), 1340(C=S) cm^{-1}.
^{1}HNMR ($CDCl_3$): δ 3.80(s, 2H, CH_2), 4.42(s, 1H, NH), 9.60(s, 1H, NH), 8.58(s, 1H, CH=N), 7.70-8.20(m, 4H, Ar-H).
^{13}CNMR ($CDCl_3$): δ 50.20, 126.47, 127.41, 128.42, 129.58, 133.74, 134.24, 142.20, 208.22, and 212.30.
MS (m/z): 279.27 (M+)

Biological Prediction Study and Analysis of Activities with PASS

The relationship between structure and different biological activities was studied using computer programme PASS. The structures of derivatives 2-(a-j)

were subjected for the predictions of their probabilities of being active [Pa] and inactive [Pi] for the selected activities. The following three activities were predicted with top probability for the series of compounds 2-(a-j).

1 Fibrosis treatment
2 Mcl-1 antagonist
3 Insulysin inhibitor

Table II: Predictions of biological activities by PASS:

Activity Comp.	Fibrosis treatment	Mcl-1 antagonist	Insulysin inhibitor
	Pa	Pa	Pa
2-a	**0.916**	**0.676**	0.566
2-b	0.893	0.499	0.447
2-c	0.897	0.608	0.521
2-d	0.885	0.559	0.554
2-e	0.874	0.501	0.514
2-f	0.894	0.603	**0.606**
2-g	0.895	0.619	0.603
2-h	0.890	0.557	0.471
2-i	0.888	0.618	0.417
2-j	0.860	0.382	0.000

CONCLUSION

Biological prediction analysis revealed that the 4-{[1-Phenyl-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2a) is predicted to be moderately active as Mcl-1 antagonist. 3-Thioxo-4-{[1-p-tolyl-meth-(E)-ylidine]-amino}-[1,2,4]triazinan-5-one (2f) can be most active in the series as Insulysin inhibitor; whereas, 4-{[1-phenyl-meth-(E)-ylidine]-amino}-3-thioxo-[1,2,4]triazinan-5-one (2a) can exhibit promising activity in Fibrosis treatment, hence it is recommended for the screening of the same activity.

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